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June 6, 2006

Josephine Pascual
Information Specialist
Darby & Darby P.C.
805 Third Avenue
New York, NY 10022

Dear Ms Pascual:

Thank you for your inquiry about the mail date for the September 1999 supplement to *Arthritis & Rheumatism.*

The mail date of this issue (volume 42, issue 9, supplement) was September 30, 1999. The page numbers were S1-S474.

The information regarding the mail date of this publication was furnished by Cadmus Journal Services, and we believe it to be reliable. At this time, however, The American College of Rheumatology makes no representation or warranty to its accuracy or completeness.

Sincerely,

Jane Diamond
Managing Editor

Frankfort, Howard

From: Pascual, Josephine
Sent: Tuesday, June 06, 2006 4:20 PM
To: Frankfort, Howard
Subject: FW: DATE of Publication

Just in case you need a electronic copy.
-----Original Message-----
From: Jane Diamond [mailto:JDiamond@rheumatology.org]
Sent: Tuesday, June 06, 2006 4:13 PM
To: Pascual, Josephine
Subject: RE: DATE of Publication

Jane Diamond, Managing Editor
Arthritis & Rheumatism
1800 Century Place, Suite 250
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-----Original Message-----
From: Pascual, Josephine [mailto:JPascual@Darbylaw.com]
Sent: Tuesday, June 06, 2006 2:33 PM
To: Jane Diamond
Subject: RE: DATE of Publication

Hi Jane,

Would it be possible to get this on a formal letter head? Please see the attachment above, this is an example it does not need to be exact, but something similar would be great. We need the letter to hand to the USPTO examiner.

Please let me know.

Regards,

Josephine Pascual
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-----Original Message-----
From: Jane Diamond [mailto:JDiamond@rheumatology.org]
Sent: Tuesday, June 06, 2006 2:20 PM
To: Pascual, Josephine
Subject: RE: DATE of Publication

It was mailed on September 30, 1999.

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-----Original Message-----
From: Pascual, Josephine [mailto:JPascual@Darbylaw.com]
Sent: Tuesday, June 06, 2006 2:18 PM
To: Jane Diamond
Subject: DATE of Publication

Hi Jane,

Please let me know the date the journal I am inquiring was mailed to your subscribers, "Arthritis and Rheumatism 42 (9 Suppl): pS233 Sept. 1999[Pascual, Josephine] .

Thanks very much for you assistance.

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GENETIC VARIATION IN APOLIPOPROTEIN H (β2-GLYCOPROTEIN I) AFFECTS THE OCCURRENCE OF ANTIPHOSPHOLIPID ANTIBODIES AND APOLIPOPROTEIN H CONCENTRATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS. M Ilyas Kamboh, Susan Manzi, Haider Mehdi, Shirley Fitzgerald, Dharambir K Sanghera, Lewis H Kuller, Christopher E Aston Pittsburgh, PA

Apolipoprotein H (apoH, protein; *APOH*, gene) is a required cofactor for the production of antiphospholipid antibodies (APA). In this study we have examined whether genetic variation in the *APOH* gene affects variation in risk for systemic lupus erythematosus (SLE), occurrence of antiphospholipid antibodies (APA), and plasma apoH concentrations. A total of 222 white SLE women were screened for four *APOH* polymorphisms (codons 88, 247, 306, and 316) by polymerase chain reaction, and for plasma apoH concentrations by ELISA. Of these, 65 (29.3%) were positive for APA (APA-positive group). None of the four *APOH* polymorphisms were significantly associated with variation in risk for SLE. The codons 306 and 316 polymorphisms showed significant, gene-dosage effects on plasma apoH concentrations ($p<0.0001$) and explained 9% and 13%, respectively, of the residual variation in apoH concentrations. Plasma apoH concentrations were significantly higher in patients positive for APA than in patients negative for APA (18.5±0.5 mg/dl vs. 17.1±0.3 mg/dl; $p=0.02$). The distribution of the Trp316Ser polymorphism was significantly different between the APA-positive and APA-negative groups. The frequency of the mutant allele (Ser316) was significantly lower in the APA-positive group than in the APA-negative group (3.1% vs. 12.1%; $p<0.04$), indicating that the Ser316 mutation is protective against the production of apoH-dependent APA. Our data indicate that common genetic variation in the *APOH* gene is a significant determinant of plasma apoH variation in SLE patients, and the Trp316Ser polymorphism appears to provide protection against the production of APA in SLE patients.

Disclosure: work reported in this abstract was supported by:

974

DO RADIOGRAPHIC PATTERNS OF HIP OA INFLUENCE THE GENETIC PREDISPOSITION IN FAMILY MEMBERS? P Lanyon, S Doherty, K Muir, M Doherty Nottingham, United Kingdom

There was no correlation between patterns of migration to affected siblings and index cases. Conclusion: The genetic influence on definite hip OA is significantly greater in families where the index case has no osteophyte compared to grades 1-3 ($p=0.019$). Patterns of femoral head migration do not 'breed true', suggesting that whilst the tendency to develop hip OA is under strong genetic influence, interaction between genetic and environmental or mechanical factors may be more important in determining the specific phenotype.

Disclosure: work reported in this abstract was supported by:

975

AN ALTERED NUCLEOTIDE SEQUENCE IN THE IMMEDIATE PROMOTER REGION OF CD40 LIGAND IS ASSOCIATED WITH RHEUMATOID ARTHRITIS. Yixin Li, Guang-Rong Sun, Mary K Crow New York, NY

CD40 ligand (CD40L) is a glycoprotein expressed on the surface of activated CD4-positive T cells. Interactions between CD40L and CD40 result in B cell proliferation, immunoglobulin production, and monocyte and dendritic cell activation, which are features observed in autoimmune diseases such as rheumatoid arthritis (RA). To explore the critical role of CD40L in RA, we have analyzed the 5' flanking sequence of CD40L. An altered nucleotide sequence in the immediate promoter region of the CD40L gene segment has been identified. This alteration is characterized by a substitution of a cytosine (C) for an adenine (A) at position -125. We have screened for the alteration among genomic DNAs isolated from RA synovial tissue samples by nested PCR using specific oligonucleotide primers. The altered sequence has been observed in more than 30% of RA patients studied, but neither in normal nor in disease control groups. The alteration has been detected in both synovial tissue and peripheral bloods from RA patients. We have further compared the promoter activities of wild-type and altered promoter segments using a luciferase reporter gene assay. Our data show that the altered promoter sequence confers a 5-fold increase in promoter activity when compared with the wild type sequence. In summary, our results correlate the altered promoter sequence of CD40L with RA and may provide a molecular basis for augmented T cell function in that disease.

Disclosure: work reported in this abstract was supported by:
Dr. Crow is a subinvestigator in a clinical trial of anti-CD40 ligand monoclonal antibody.

976

THE GENETIC CONTRIBUTION TO RAYNAUD'S PHENOMENON: A POPULATION-BASED TWIN STUDY. A J MacGregor, I K Cherian, L Carter, C M Black, T D Spector London, United Kingdom

Objective: To assess the relative contribution of genetic and environmental factors to Raynaud's phenomenon (RP) by examining its distribution in monozygotic (MZ) and dizygotic (DZ) twins ascertained in a population sample.

Methods: A two-stage strategy was used to assess the occurrence of RP. First, questionnaires were mailed to a sample of 3,652 individuals comprising 911 MZ and 915 DZ pairs from a national twin register to document the prevalence of digital colour changes. All were female-female twin pairs between the ages of 30 and 60 years. Second, a representative sample of respondents was interviewed and examined by a nurse metrologist experienced in the assessment of RP. Physiological digital cooling and rewarming responses were assessed thermographically in these subjects using a standard cold challenge test.

Results: Questionnaire responses were obtained from a total of 702 MZ and 727 DZ pairs (response rate 83%). Among these, the prevalence of RP (defined as a history of two or more digital color changes including white) was 11%. The casewise concordance for RP was significantly higher in MZ when compared with DZ twins (MZ: 38%; DZ: 18% $p<0.01$), equivalent to a heritability (H) for RP of 55% (95% CI: [41%, 68%]). A total of 163 pairs were assessed by cold challenge. A genetic contribution was found for (a) baseline skin temperature (H=76%) (b) initial fall in temperature (H=44%) and (c) rate of rewarming (H=32%).

Conclusion: This is the first study to assess the genetic basis of RP in the population. The findings show conclusively that there is a substantial genetic contribution both to the symptoms of RP and to the associated vascular changes.

Disclosure: work reported in this abstract was supported by:

977

AN HYDROPHOBIC SEQUENCE AT POSITIONS 313-316 (Leu-Ala-Phe-Trp) IN THE FIFTH DOMAIN OF APOLIPOPROTEIN H (β2-GLYCOPROTEIN I) IS CRITICAL FOR CARDIOLIPIN BINDING. Haider Mehdi, Asma Nasir, M Ilyas Kamboh Pittsburgh, PA

[illegible] charged antibodies in [illegible] ally occurring [illegible] he binding of [illegible] ry conserved [illegible] id to interact [illegible] quence in its [illegible] mutation, we [illegible] site-directed [illegible] l mutant type [illegible] id by capture [illegible] don of apoH [illegible] rant and wild [illegible] mutant types [illegible] by, Phe315Ser [illegible] ation showed [illegible] ee of the four [illegible] main of apoH [illegible] is critical for its binding to [illegible]

Disclosure: work reported in this abstract was supported by:

978

A GENOME SCAN IN A MURINE MODEL OF RHEUMATOID ARTHRITIS LOCALIZES LOCI ASSOCIATED WITH DIFFERENT TRAITS AND GENETIC BACKGROUNDS. Jeffrey M Otto, Katalin Mikecz, Alison Flanagan, Edit I Buzas, Gabriella Cs-Szabo, Jill T Enders, Tibor T Glant Chicago, IL

Proteoglycan-induced arthritis (PGIA) is a murine model for rheumatoid arthritis (RA) both in terms of its pathology and its genetics. PGIA can only be induced in susceptible murine strains and their F2 progeny. As with RA, the genetics are complex and recessive, containing both MHC and non-MHC related components. We report here the genome wide screening for arthritis-associated loci, using F2 hybrids of susceptible (BALB/c and C3H/HeCr) and non-susceptible (DBA/2, and C57BL/6) strains of mice. Three different groups (n=144; BALB/c X C3H/He,n=48; BALB/c X C57BL/6,n=48 and BALB/c X DBA/2,n=48) of F2 hybrids were immunized for PGIA and subjected to an exhaustive genome wide screen with 106 separate polymorphic markers. Additionally, we analyzed these mice for various biochemical and immunological markers such as serum antibodies (both hetero and auto), soluble cd44, interleukins 1 and 4, interferon-γ, antigen stimulation of T-cells and T cell proliferation. None of these markers demonstrated a statistical linkage with PGIA. However, there were marker differences not only between arthritic and non arthritic individuals, but also between the different genetic backgrounds. For instance, all mice of the BALB/c X C3H/HeCr cross possessed auto-antibodies with an arthritis incidence of 56%. This was unexpected as both strains are susceptible to PGIA. In contrast with mice of the C3H background, the other two crosses had lower auto-antibody levels (42% of the C57Bl/6 background and 35% of the DBA/2 background) and a lower arthritis incidence(27% and 33% respectively). Additionally, we found a strong correlation ($p<0.0001$, $cor=0.739$) between auto-antibody and hetero-antibody levels in arthritic mice. Using these different crosses and the different biochemical marker data we have identified multiple loci associated both with the different genetic backgrounds as well as with the different traits we tracked in PGIA.

Disclosure: work reported in this abstract was supported by:

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Inventor: Mary K. Crow

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